AMERICAN JOURNAL OF PHARMACY

and

THE SCIENCES SUPPORTING PUBLIC HEALTH

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NOVEMBER
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OUR COVER

MAHLON N. KLINE

1846-1909

MAHLON N. KLINE is a name well remembered in pharmacy as one closely associated with the development of the drug industry in the United States. He possessed those attributes and reflected those qualifications which still cause observers to claim that it was indeed his generation who represented the "Golden Age" of Pharmacy.

Mr. Kline was President of the National Wholesale Druggists' Association in 1885 and was for many years chairman of its most important committees. President of the Philadelphia Drug Exchange in 1884, he was one of the founders of the Trade's League, afterwards the Philadelphia Chamber of Commerce.

With Mr. Howard B. French he made possible the purchase and donation of the famous Martindale Herbarium now at the Philadelphia College of Pharmacy and Science.

One of his unusual distinctions was the tribute paid to him by Dr. Harvey W. Wiley, pioneer in Food and Drug Legislation, who stated that "he owed more to Mr. Kline in the framing of the regulations in the Law of 1906 than to anyone else."

Mr. Kline is succeeded by his son, C. Mahlon Kline, who too serves pharmacy in many ways with distinction.

EDITORIALS

THE REAL OBSTRUCTION IN THE ERADICATION OF SYPHILIS

On this page the Editor expresses his views regarding the control of one of America's serious disease problems.

ONE of the most pertinent findings resulting from the examination of the first million selectees and volunteers under the Selective Service Act is the astounding prevalence of venereal disease. In the October 18th issue of the *Journal of the American Medical Association,* R. A. Vonderlehr and L. J. Usilton report that 45.2 cases of syphilis per thousand were observed, with tremendous variation in different geographical areas. Thus, in North Carolina, a rate of 170 per thousand was recorded, whereas only 5.8 per thousand was found in New Hampshire. This great difference might be explained in part, at least, by the fact that the ratio of negroes to whites having syphilis was 13 to 1. So much for statistics.

It is a well known fact that, when properly treated, syphilis is nearly always curable and it can invariably be rendered non-infectious insofar as others are concerned. The difficulty is that persons having syphilis may or may not accept treatment as they wish and even if proper treatment is instituted they may discontinue it at any time *even if they still are a potential source of infection for others.*

It is our contention that a syphilitic should be forced to continue treatment at least until all danger to others is removed. Some will argue that this is in violation of an individual's rights but it is not any more so than the well-accepted regulation requiring quarantine in cases of smallpox or scarlet fever. The old days in which the contact between physician and patient was inviolate are past and the rights of society are indeed more to be considered than those of the individual.

Actually a person at large with a case of smallpox is in some respects less dangerous than an untreated syphilitic in the highly

infectious stage. The general public is universally protected to a degree against the former by vaccination whereas no immunization technic is practiced to guard one against syphilis.

There are many in the field of public health who look with great disfavor upon state medicine and indeed much can be said against such a radical change in our American system, but it is the failure of many of our organizations in the public health professions to remedy such obvious weaknesses in the present system which lends argument to the proponents of such radical programs.

There is no reason for syphilis being as widespread as it is. Smallpox, by universal control measures, has been practically eliminated from those states where vaccination is compulsory. Syphilis, also, can be likewise eradicated if we face the facts, propose the necessary legislation, and then co-operate in its enforcement. The way to combat disease is at its source and not content ourselves with feeble efforts directed at isolated cases. A syphilitic when detected should become the ward of the state, on probationary freedom until he is discharged by a competent physician as no longer a menace to society. By such methods the life, health and happiness of millions as yet unborn may be insured against the ravages of one of the most detestable diseases known to man.

L. F. Tice

SOIL

I am the leavened dust of ageless rocks,
The mould of passing men and trees and worms,
Returned to circulation:
I am the lull in life,
And teeming with tomorrows yet to be;
Partner to sun, and sensitive to rain.
I am the warp and woof of life;
Or truer still, the womb,
Whence, after rest, Life sallies forth
To walk its mile—and rest again.
I breathe with seasons, hide beneath the snow
But through the frost, rehearsals come and go
And Spring arrangements made, and Summer, Fall
For supervision of their growth is mine.
Within the great, round plan, Divine
And there are those who call me clay
—But wait,—
For I am only clay until I grow a rose!
A rose whose beauty is a secret of the Sun and I,
And ultimately lifts itself to Heaven;
That Heaven where all of beauty is conserved.
    But what of You—O Shape of Clay
    Have roses ever grown in you
    To glorify the little part of you
    That has entitlement to Heaven?
    And do you know that some soon day
    Your dust will be again a part of me
    As I am now a part of you?
I am the whole container of the dead
And sole retainer of the urge to live,
I am the leavened dust of ageless rocks,
The dust of passing men and trees and worms,
Returned to circulation.
    For I am soil, sweet earth, clean earth
    The dregs of death
    And harbinger of birth!

IVOR GRIFFITH

THE DRUG INDUSTRY'S CONTRIBUTION TO MEDICAL CARE AND TO THE PROGRESS OF SCIENCE

The following is an address delivered by the author before the Scientific Session on the occasion of the centennial celebration of the School of Pharmacy, University of Maryland, Baltimore, June 4, 1941. The reader will find in this article a clear and concise description of the tremendous changes brought about in the drug industry in the last century and also a much better appreciation of the present status and future trends to be expected.

By Dr. Robert P. Fischelis

ON the occasion of the one hundredth anniversary of the founding of the Maryland College of Pharmacy it would perhaps be fitting to review in detail the development of the drug industry of the United States from its humble and more or less individualistic beginnings to its present mechanized and highly specialized state. However, time permits of only a cursory review and the recording of a few landmarks in the century of progress.

In 1841 the retail pharmacy was still the primary source of prepared and specially compounded medicines. Progress in the basic sciences and in the methods of medical care since that day has been so rapid that the individual pharmacist, although more highly educated and more scientifically trained, must of necessity function in a more restricted sphere. In other words, pharmacy, as well as medicine, has become more highly specialized.

One of the first steps toward specialization in modern medicine was the early division of labor between physicians and pharmacists. With the advance of medical science, less and less reliance was placed on the incantations and mystical brews upon which the "medicine man" of an earlier day had depended for his healing art. In course of time, the preparation as well as the use of drugs and medicines reached a scientific basis, and the practice of pharmacy itself became a specialized field of medical care. Pharmacists today occupy not only the important position of producers, compounders and distributors of drugs and medicines, but they also originate drugs based upon specifications of the medical profession.

Many functions of the pharmacist of 1841 have been absorbed by the drug manufacturer of 1941. The individual apothecary no

longer makes up in his laboratory all the pills, elixirs, tinctures and extracts of an earlier day, nor does he attempt to produce the multitude of newer preparations which physicians prescribe today. The professional function of the pharmacist has not changed, but the base of many operations has been moved from the laboratory of the drug store to the production line of the manufacturing house.

The early apothecary, working in his shop, was manufacturer, compounder and dispenser, all in one. There was no division of labor in the modern sense. As a result, some of these apothecaries became earnest research workers, delving into the mysteries of chemistry and endeavoring to ascertain the active principles of the crude drugs then in use. Carl Wilhelm Scheele, who discovered oxygen, chlorine, hydrofluoric and prussic acids, and glycerin; Frederick Sertuerner, who discovered morphine; Pelletier and Caventou, who discovered quinine; and others who by important discoveries in inorganic and organic chemistry laid the foundation of the vast synthetic chemical industry, were all pharmacists either in their early days or throughout their lives. In more recent times, pharmacists ambitious to carry on laboratory research have drifted quite naturally into the specialized fields of science such as chemistry, pharmacology or bacteriology and have become identified with these and other branches of medical science rather than with pharmacy, in its more restricted activities.

"From Materia Medica to Pharmacology"

At the time of the founding of the Maryland College of Pharmacy there was in existence a very extensive list of drugs with a background based upon clinical rather than scientific evidence of usefulness. "The long struggle between the Galenists, who believed that all the valuable remedial agents were the products of plant or animal origin, and the Alchemists, who believed that the only useful remedies were minerals that had been refined in their retorts and crucibles, had been compromised long since, and the materia medica of that day included large numbers of substances from both sources," (1) with synthetic organic compounds gradually coming into the picture.

"If we ask how the various drugs in the materia medica of that day came to be there," says Dr. Carl A. Dragstedt in his delightful little essay entitled "From Materia Medica to Pharmacology," (1)

1. "From Materia Medica to Pharmacology" by Carl A. Dragstedt, M. D., Northwestern Bulletin, Vol. XLI, No. 3, November 11, 1940.

"the answer may be illustrated in part as follows: Cinchona Bark was there because an earthquake threw some cinchona trees into a lake adjoining a village, and a sick Indian, unable to walk far enough to get better water, was forced to drink the bitter water from the lake and thereupon got well. Ergot was there because the European peasants were forced by economic circumstances to eat rye bread made from tainted flour. Digitalis was there because an inquiring physician listened to an old woman's story. Atropine was there because a pharmacist's apprentice rubbed his eyes while he was filling a prescription. Strophanthus was there because the botanist on David Livingstone's expedition kept his toothbrush in his pocket, where it got contaminated with an arrow poison he had obtained from the natives. Epsom Salt was there because a farmer had a spring on his property, from which his cattle refused to drink. His curiosity persuaded him to try it and its pharmacological effects were promptly called to his attention."

Today the pharmacologist is relied upon to supply accurate data on the action of prospective drugs, based upon animal tests in the laboratory, in advance of their clinical trial upon man. Medicines are literally made to order, but not in the sense of merely mixing a number of drugs to accomplish some specific therapeutic action, as was the case with the shotgun prescription of an older day. By means of highly refined processes in the laboratory of the organic chemist, compounds of complex structure with a maximum of specific therapeutic action and a minimum of undesirable side actions are built up from their elements. Such achievements are the result of the coordinated effort of pharmacologists and chemists, many of whom carry on their activities in the research laboratories of the drug industry.

The conquest of pain, the prevention of infectious diseases by the destruction of disease-producing bacteria outside of the body and the development of immunizing sera and preventive vaccines, the soothing of excited nervous systems, the cure of diseases brought on by nutritional deficiencies, and the direct destruction of micro-organisms and their toxins in the blood stream have all been accomplished to a greater or less extent in man's continuous fight against disease. The chapters of medical history which record the progress in this field are still open to revision but occasionally there appears a gifted writer like Slosson, or DeKruif, or Silverman who can dramatize the simple story of patient and laborious research in uni-

versity, state, industrial, or research foundation laboratories which, through the interchange of information by means of our modern systems of reporting and recording, finally lead to the construction of what Milton Silverman has so aptly referred to as the "Magic in a Bottle," (2) emanating from the laboratories of the pharmaceutical manufacturer and the prescription room of the pharmacy to bring relief or cure to sufferers everywhere.

The Conflict Between Science and Commerce

While it is possible to write a fascinating story of the contribution of the drug industry to the progress of medical science, there have been and are unfortunate limitations to these contributions because of the dual nature of these enterprises. On the one hand, splendid laboratory facilities for production are made available and competent scientists are engaged in research and developmental work. On the other hand, the fact that stockholders look for dividends from their investments has a tendency to limit the extent of altruistic effort. Furthermore, the clinical experimentation which is essential to the establishment of the real value of a drug cannot be, or, at least, has not been done in the drug industry. It has been necessary for individual manufacturers to establish their own clinical contacts. Some have done this for years through friendly private practitioners or hospital contacts. Others have done it by creating fellowships at medical centers or establishing foundations for clinical research. Progress in cooperation between some of the better established and well financed units of the drug industry and outstanding clinicians has been very marked in recent years and there are signs of the possibility of more intimate relationships between producers of drugs and recognized clinicians in the future which will undoubtedly promote progress in this field.

Obviously, the producer of drugs is also expected to be a source of information regarding them. Before a curb was placed upon the enthusiasm of the advertising departments of the drug industry by such agencies as the Council on Pharmacy and Chemistry of the American Medical Association and the Food and Drug Administration even the most conservative members of the industry were apt to be extravagant in their claims of therapeutic efficiency for products bearing their own label. It was this situation which undoubtedly

2. The Macmillan Company, New York.

brought forth such criticism as was voiced in an address on "Chauvinism in Medicine" delivered before the Canadian Medical Association September 17, 1902 (thirty-nine years ago) by the late Dr. William Osler, then professor of medicine at Johns Hopkins University. He paid his respects to certain segments of the drug industry in the following paragraphs:

"The practitioner must be kept out of the clutches of the arch enemy of his professional independence—the pernicious literature of our camp followers, a literature increasing in bulk, in meretricious attractiveness and in impudent audacity. To modern pharmacy we owe much, and to pharmaceutical methods we shall owe much more in the future, but the profession has no more insidious foe than the large borderland pharmaceutical houses. No longer an honored messmate, pharmacy in this form threatens to become a huge parasite, eating the vitals of the body medical. We all know only too well the bastard literature which floods the mail, every page of which illustrates the truth of the axiom, the greater the ignorance the greater the dogmatism. Much of it is advertisements of nostrums foisted on the profession by men who trade on the innocent credulity of the regular physician, quite as much as any quack prays on the gullible public. Even the most respectable houses are not free from this sin of arrogance and of ignorant dogmatism in their literature. A still more dangerous enemy to the mental virility of the general practitioner, is the 'drummer' of the drug house. While many of them are good, sensible fellows, there are others, voluble as Cassio, impudent as Autolycus and senseless as Caliban, who will tell you glibly of the virtues of extract of the coccygeal gland in promoting pineal metabolism, and are ready to express the most emphatic opinions on questions about which the greatest masters of our art are doubtful. No class of men with which we have to deal illustrate more fully that greatest of ignorance—the ignorance which is the conceit that a man knows what he does not know; but the enthrallment of the practitioner by the manufacturing chemist and the revival of a pseudo-scientific poly-pharmacy, are too large questions to be dealt with at the end of an address."

Today the literature issued by pharmaceutical manufacturers, although not perfect, clearly shows the restraint imposed by the more conservative scientific element within the industry and the effect of regulatory procedures.

Goodman and Gilman, in their recently published text entitled "The Pharmacological Basis of Therapeutics," (3) state that "a drug may be broadly defined as any chemical agent which affects living protoplasm, and a few substances would escape inclusion by this definition."

For control and regulatory purposes the definition of the term drug is much more prosaic and circumscribed. Our latest Federal law states that "the term drug means articles recognized in the official United States Pharmacopœia, official Homeopathic Pharmacopœia of the United States or official National Formulary, or any supplement to any of them; and articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals; and articles intended for use as a component of any articles specified in the foregoing; but does not include devices or their components, parts or accessories."

A study of these two definitions is a good example of the difference between the approach of the scientist and the policeman to the problems of the drug industry. These definitions also furnish the basis for a text on the drug industry's contribution to the progress of science as applied to medical care. Acceptance of the definition that a drug is "Any chemical agent which affects living protoplasm" immediately establishes a basis for scientific research in the drug industry which is deeply rooted in biology, physics and chemistry. It also establishes the basis for the support of research in pure as well as applied science by the drug industry. The legal definition and the Food, Drug and Cosmetic law itself and particularly the regulations promulgated by the enforcement agency, furnish the best indication of the abuses which have crept into the drug industry, for they have been devised to curb these abuses.

Origin of the Drug Industry

The oldest pharmaceutical manufacturing establishments in the United States had their origin in retail pharmacies. It is interesting to trace the history of these establishments, pioneered either by physicians or pharmacists or pharmaceutical chemists who became quantity producers of pills, tinctures, fluid extracts, extracts and other dosage forms of the drugs of their day and then, by a combination of business

3. The Macmillan Company, New York.

acumen, alertness to the progress of medical science, ingenuity in devising production equipment and a vision of improved service to humanity, grew to be imporatnt allies of the medical profession in the fight against disease.

Of course, there are manufacturers of drugs who have never passed beyond the stage of becoming merely large scale producers of ordinary combinations or dosage forms of drugs and who have no ambition to move into a more productive sphere. Others have seen in improved and increased facilities the opportunity for extending their service to humanity by collaborating with those engaged in extending the frontiers of the medical sciences, chemistry, pharmacology, bacteriology and immunology, as applied to medical care.

To these far-seeing individuals we owe the splendidly equipped research laboratories of the drug industry which have sprung up in recent years to take their place in the advancement of fundamental research and to aid in taking the long step from the first laboratory recognition of the possible existence of a new therapeutic agent to its ultimate distribution throughout the world in a pure, stable and accurately standardized form.

Adrenalin, Insulin, Thyroxin, Liver Extract, the Vitamins and Hormones could not have been made as readily available to the sick in all income groups without the ability of the drug industry to promptly place a laboratory curiosity on a mass production basis in forms for ready and safe administration.

If we take for granted the well-known contributions of the pharmaceutical industry to the engineering of large scale production and to the economics of production, we may pass to the broader relations of the industry to the general progress of science and to the improvement of medical care.

Development of Drug Standardization

Perhaps the first important contribution of the pharmaceutical manufacturing industry to scientific progress as applied to medical care was the effort to standardize the potency of the drugs supplied by devising laboratory methods of estimating their strength and purity. Possibly the urge toward standardization was as much a matter of self-defense and economics as it was a matter of interest in the consumer. A manufacturer who purchased quantities of belladonna root or leaf having a high alkaloidal content or digitalis leaf having a high potency, could better protect his reputation and pos-

sibly profit in dollars if he knew the actual alkaloidal or glucosidal content of the drugs he purchased and was therefore in a position to adjust his preparations to a given standard. The perfection of methods of estimating drug constituents was, therefore, subject to a double incentive. In the first place there was the achievement of uniformity in the interest of proper dosage and effect upon the patient and, secondly, there was the economic advantage of producing increased quantities of finished drug products from high potency raw materials.

Manufacturing pharmacists have contributed methods of standardization of drugs ranging from the simple determinations of quantity of extractive, through chemical assays of content of alkaloidal and other active principles to the more complex biological assays for such drugs as ergot, digitalis and strophanthus, and antitoxic sera, vaccines, vitamins and hormones. The assay and standardization of drug products is a comparatively recent development. It did not receive serious consideration until the start of the present century. Since the passage of the first Federal Food and Drug Act of 1906 the contributions of the analytical laboratories of drug manufacturers to the inclusion of satisfactory standards for drugs in the U. S. Pharmacopœia and National Formulary constitute a major chapter in the history of drug standardization. The methods devised cover physical, chemical and biological tests and reflect the ingenuity of those engaged in the work of evaluating the quality of raw materials and the accuracy of manufacturing methods.

The contributions to drug standardization made by individual laboratories and the workers in those laboratories could, of course, be cited. They are recorded in the chemical and pharmaceutical journals and in the circulars of the sub-committees of the U. S. Pharmacopœia Revision Committee and the National Formulary Committee. These records indicate a never ending search for more specific, for simpler and for more accurate methods of measurement of activity, identity, purity and strength of the products offered for use in the diagnosis, prevention and cure of disease.

The establishment of control laboratories in the larger manufacturing houses has spread to such an extent as to include practically every concern which produces drugs in any quantity and it has led to arrangements for control by private analytical laboratories in cases where the operations are not sufficiently extensive to warrant establishment of a control laboratory within the manufacturing plant itself.

Facilities for biological assaying required of drugs like digitalis, aconite, epinephrine, ergot, pituitary, vitamins and hormones are less frequently encountered in manufacturers' laboratories but care is taken to provide for such service through contact with competent university or private laboratories.

Regulatory provisions under federal and state laws are such today that manufacturers simply must provide for control of the products they place on the market. Once a control laboratory has been organized, it takes on duties which include not only the testing of raw materials and finished products, but also the protection and improvement of manufacturing processes and techniques and studies of methods of preservation and packaging, all of which contribute greatly to the progress of pharmacy and the care of the sick, especially when there is interchange of information between the various manufacturing laboratories such as is provided through the drug manufacturers' associations.

Research in the Drug Industry

A somewhat different line of activity results from embarkation upon what may be termed "pure research," which is undertaken in the expectation that there may be developed some new drug or modification of an existing drug which will bring to the producer an exclusive proprietorship either as the result of patentability or priority of manufacture. It is in the development of research departments in the drug manufacturing industry and the products of such researches that competitive effort is today most greatly manifested. But no drug developed in a pharmaceutical manufacturing laboratory can reach any degree of prominence without the cooperation of the medical profession.

Chemical laboratories can produce thousands of compounds while pharmacologists are testing a hundred. Clinicians are skeptical about the use of any drug until laboratory findings on suitable test animals have clearly established its safety and possible effectiveness. It was the lack of due care in establishing the complete safety of new drugs or dosage forms of such drugs which led the federal government to enact into law a restriction on the marketing of new drugs until after an application has become effective. This application made to the Food and Drug Administration must, in order to become effective, be accompanied by sufficient clinical data and information as to control to establish its complete safety for use as prescribed.

Viburnum, Guarana, Coca, Jaborandi, Grindelia, Saw Palmetto, Convallaria, Cocillana, Kamala, Cascara Sagrada, Tonga and Ephedra are a few of the vegetable drugs introduced to medicine at various times in the past century chiefly on the responsibility of manufacturers and without governmental supervision. Many of these drugs hark back to the days of "materia medica" and empiricism. Only a few would pass muster if introduced in the era of "pharmacology."

With the advent of serums, vaccines, bacterial vaccines and potent chemotherapeutic agents administered parenterally, the United States Public Health Service was assigned the duty of passing upon the facilities of the producer and the safety of the product under a Federal licensing system.

The subsequent development of potent chemotherapeutic agents for administration by mouth or parenterally, such as the sulfonamide derivatives and the careless dispensing of sulfanilamide dissolved in diethylene glycol, with the resultant loss of life, gave emphasis to the need of some form of control over the promiscuous production and distribution of dangerous drugs. The new drug section of the Federal Food, Drug and Cosmetic Act is the answer.

New Drug Control

Whenever a new drug with more or less specific therapeutic properties is developed, a host of imitations, variations and substitutes is made available from competing laboratories. In one sense this is not detrimental because the work of many laboratories concentrated upon the production of a drug whose efficacy has been established may well lead to improvements which will enhance its value in the hands of the medical profession. In another sense, however, senseless duplication purely for the benefit of the individual producer complicates distribution and results in duplication of stocks, confusion on the part of the practicing physician, and increased expense to the sick.

Under the patent laws of the United States it is possible to patent drugs both as to process and product. Attempts have been made to rid the system of patenting drugs and continuing proprietary rights in them by skillful use of the trade mark laws, of its abuses. To some extent this has been accomplished through public pressure to make new discoveries for the treatment of disease available as promptly as possible after announcements of the discovery of such drugs have been made in the public press.

Patents have been issued for some drug products or processes which have yielded their holders handsome revenues and have more than repaid the investment in research and clinical testing. On the other hand, it is said of the development of certain sulfonamide compounds that manufacturers who pioneered in this field have not been able to recover the expense of their researches in the production of these products due to premature redcution in costs to the consumer as a result of keen competition. Where the patent rights are shared by several firms and where the raw material is made available without license to manufacturers generally, a product quickly loses its classification as a proprietary "specialty." This is all to the good for the consumer but rather hard on the producer, who may have sunk considerable sums into the laboratory work and clinical testing involved in establishing the value of the drug.

Social Aspects of the Industry

Considerable discussion has occurred at various times about the advisability of dedicating all patents affecting the cure of disease, to the public. This is in line with the discussion of the status of the drug industry as a public utility rather than a source of private profit. Those who argue that the sick should not be exploited either by the medical profession or by the drug industry, or by any other group that profits from medical care, hold that "nationalization" of the drug industry, which is a less significant term perhaps than "socialization," should be accomplished in the public interest. Definite expression of this concept is given in the volume entitled "Health Insurance" (4) by Louis S. Reed, an economist for the United States Public Health Service. He states that, "nationalization of the industry would bring the following advantages:

"(1) Only drugs and preparations of value in the prevention and treatment of disease would be produced and made available to the medical profession and the public.

"(2) By elimination of duplicate preparations and competitive and useless advertising and sales promotion activities, costs of manufacture and distribution could be lowered considerably.

"(3) At a cost of a fraction of the amount saved through the elimination of present wastes, sound information could be given the public on the care of health.

"(4) Announcement to the medical profession of new drugs and preparations would come from scientific and disinterested sources.

4. Harper and Brothers, New York.

"(5) There would be more and better organized pharmaceutical research than at present.

"The purpose of the drug industry," says Dr. Reed, "should not be to provide incomes for the producers. Its purpose should be to provide the public and the medical profession with drugs and medicines needed for the prevention and cure of sickness, at the lowest possible cost. For their efforts in this direction producers are entitled to a reasonable return. Considered from this viewpoint the drug and medicine industry as now conducted is an economic monstrosity. The production and distribution of drugs and medicines is now conducted in a fashion as idiotic as trial by combat, as irrational as the treatment of disease by witchcraft and devil exorcism. Were this essential activity to be rationally organized, the country's drug bill could be cut by 65 per cent., with an appreciable gain in health, lowered sickness, and less mortality."

That the drug manufacturing industry itself is none too well satisfied with the conduct of its own members may be gleaned from the following resolution passed by the American Drug Manufacturers Association:

"RESOLVED, By the members of the American Drug Manufacturers Association in annual convention assembled, that they subscribe and adhere to the following principles as an expression of a Code of Ethics:

"First: The essence of ethics is honesty.

"Second: Whatsoever ye would that men should do unto you, do ye even so unto them.

"And WHEREAS, It is the desire of the membership of the American Drug Manufacturers Association to go on record with reference to certain definite practices, be it

"RESOLVED, That it is the sense of this Association that it is unethical:

"First: To knowingly produce an imitation of a specialty offered by a competitor; therefore, the marketing of a colorable imitation of any competing product is to be highly condemned.

"Second: To pass off the products of one manufacturer for those of another by imitation of products, labels, packages or special designs, by simulation of advertising or trade names; by the appropriation of the results of a competitor's research, ingenuity, labor and expense, thereby avoiding costs otherwise necessarily involved in production.

"Third: To make, as a private formula, any product which a salesman or customer may request as an imitation of a specialty introduced by another manufacturer.

"Fourth: To permit salesmen to offer a product as a substitute for a specialty introduced by another manufacturer.

"Fifth: To make, or permit employees to make, false or disparaging statements respecting competitors' products, their business, finances, credit or integrity, and

"Be it further RESOLVED, That the members of this association denounce and condemn in the strongest terms any form of piracy or the practice of duplication in color, description, or design, that would tend to deceive the buyer or the public so as to lead them to believe that in purchasing said imitation they were getting the original article, since a manufacturer, who through genius, advertising efforts or reputation has built up a trade on any article so that it has become generally known by its color, design or construction, though it may not be patented, is entitled to the same consideration and reward as though it were in fact patented."

Enough has been said in this paper to show rather clearly that the drug industry has kept pace with the progress of the times and that it is conducted by human beings who are subject to all the ambitions, emotions and fallibilities common to the genus homo. Industrially it ranks high among the producers of wealth in the United States. Professionally, at times and places, it reaches the highest concept of the ethical ideal in the practice of medicine. Its place in the field of medical care is made most difficult because its services are rendered through products rather than personal ministration. Yet its leaders have caught the significance of the scientific approach to the conquest of disease and there is abroad in the industry the spirit so well portrayed in the closing paragraphs of Silverman's fascinating story of the development of quinine, morphine, cocaine, digitalis, the barbitals, the vitamins, the hormones and the sulfonamides.

"Some day," says Silverman, "there will be more chapters to this story of drugs. Scientists have invested six thousand years in their search for good drugs, but men still sicken and die needlessly. The scientists certainly won't stop now.

"Even today, these stories of the future are being lived. Somewhere is an old physician, weary from years of ministering to his patients, who has found a strange clue, 'It is odd,' he writes to a

university scientist, 'that an old pet medicine of mine should cure so many patients. How about driving up here for the week end?'

"Somewhere is a man who says, 'If I could only get a nitrogen inside that phenanthrene nucleus and then couple some acetyl groups on the double bonds and then . . .'

"Somewhere someone is wondering, 'Now what would happen if I'd shoot some of that new extract into monkeys instead of guinea pigs. Monkeys are more like men.'

"Somewhere some young fellow is pleading into a laboratory telephone, 'I know, darling, and dammit I'm sorry about dinner. But I want to start one more batch of mice. I think I've got something . . .'

"Somewhere tomorrow's triumphs are in the making, as fantastic as a fairy tale or as simple as ABC. Some day they, too, will be magic in a bottle."

OUR CONTRIBUTORS THIS MONTH

Robert P. Fischelis, B. Sc., Phar. D., is secretary and chief chemist of the Board of Pharmacy of the State of New Jersey. Long active in the affairs of pharmacy, considerable credit is due him for raising the professional standards of pharmacy not only in New Jersey but nationally. As a member of the Board of Health of the State and a director of the American Social Hygiene Association, Dr. Fischelis renders invaluable service in placing pharmacy in its proper position as one of the public health professions.

Joseph Rosin, B. Sc., Ph. M., is chief chemist of Merck and Company. A diligent worker in pharmaceutical chemistry, he has made many contributions to the chemical and pharmaceutical literature. His work in behalf of Pharmacopœial Revision is of inestimable value due to his wide knowledge of chemicals. This is well illustrated in his book *Reagent Chemicals* and the *Merck Index* which is largely the product of his pen. H. Rosenblum and H. Mack are co-workers at Merck and Company and colleagues of the senior author.

ASSAY METHODS FOR 2-METHYL NAPHTHOQUINONE (Menadione)

The U S P XII will contain a monograph "Menadione" recognizing 2-methyl naphthoquinone under this title. The vitamin K activity of this compound is even greater than the original K_1, the phytyl derivative, and assay methods for its evaluation are of timely interest. The author presents both an oxidation-reduction method as well as one depending upon bromination.

By Joseph Rosin, H. Rosenblum and H. Mack

THE discovery by Dam of the anti-hemorrhagic (blood clotting) principle, Vitamin K_1, and the elucidation of its structure as 2-methyl-3-phytyl-1,4-naphthoquinone, led to the investigation of other quinones for vitamin K activity. This resulted in the finding that 2-methyl-1,4-naphthoquinone or, for short, 2-methyl naphthoquinone ($C_{11}H_8O_2$), possesses even greater vitamin K activity than the phytyl derivative. The greater activity is probably accounted for by the smaller molecular weight of 2-methyl naphthoquinone, the phytyl group being only "ballast" and does not contribute to the activity. The 2-methyl naphthoquinone compound has two advantages over Vitamin K_1: First it is a solid, crystalline substance and easy to handle, whereas Vitamin K_1 is a thick viscous liquid, difficult to handle pharmaceutically; second, it is much less expensive.

The 2-methyl naphthoquinone to which the name menadione has been assigned by the A. M. A., and which name will hereafter be used in this paper, is now on the list of recognized valuable drugs and is slated to become official in the next revision of the Pharmacopœia. A method of assay for this drug, therefore, seems in order and desirable.

Quinones are readily reducible substances. Upon reduction they yield hydroquinones which are capable of being reoxidized to quinones. These properties are the basis of assays for menadione proposed by Pinder and Singer (1) and by Trenner and Bacher (2).

Pinder and Singer dissolve the menadione in a mixture of alcohol and glacial acetic acid, partially neutralize with sodium carbonate,

buffer with Rochelle salt, and titrate with titanium trichloride, using potassium indigo-disulfonate as indicator. Titanium trichloride is extensively used for the quantitative determination of many dyestuffs, but in pharmaceutic laboratories it is, at most, only occasionally called for, and because of its instability and need for daily restandardization the use of it is unattractive.

Trenner and Bacher dissolve the quinone in *n*-butanol, reduce it with hydrogen in the presence of a special catalyst and phenosafranine (the latter serving as an indicator for the completeness of reduction) then titrate with a standardized solution of 2,6-dichlorophenol-indophenol. This method requires a complicated apparatus and a specially prepared catalyst. It is very useful, however, for determination of micro-quantities.

We have developed two methods for the determination of menadione. Method I is an oxidation-reduction method, but the process is simple and can be performed with apparatus and reagents available in any laboratory. Method II is a bromination method. We found that under conditions described later on, menadione takes up quanitatively two bromine atoms when its solution in carbon tetrachloride is treated with tenth-normal bromine.

Experimental

Method I—In this method the menadione was dissolved in glacial acetic acid, diluted hydrochloric acid and aluminum or zinc added, and after the reduction of the quinone was completed the solution was titrated with tenth-normal or fiftieth-normal ceric sulfate, using orthophenanthroline as the indicator. In our first experiments with this method we used aluminum wire. After reduction, which generally required about 1½ hours, the liquid was decanted into a flask, the wire and the vessel in which the reduction was made quickly washed with several 5 cc. portions of distilled water, then the solution titrated with tenth-normal ceric sulfate. The results by this method were a little high, as shown in Table I, due, apparently, to the presence of fine particles of either aluminum or the impurities of aluminum in the decanted solution. The decanted solutions were usually somewhat turbid.

Reduction with aluminum without filtration

Sample No. 2112	101.69%
	99.91
	100.13
	99.73
Sample No. 2704	99.98
	100.14
Sample No. 4725	99.53
	99.48
Sample P. R. S.	101.62
	98.80

Table I

We then resorted to filtering the reduced solution. This gave more correct and more uniform results as shown in Table II.

Reduction with aluminum and filtration

Sample P. R. S.	98.81%
	98.71
Sample No. 2704	98.86
	99.02

Table II

We subsequently found zinc powder (zinc dust) to be superior to aluminum for this purpose. The reduction with zinc is accomplished in less time than with aluminum and a blank consumed practically no ceric sulfate, whereas with aluminum the blank amounted to 0.3-0.5 cc. of tenth-normal ceric sulfate. Another advantage of the zinc is that after reduction, the solution, except for the excess of agglomerated zinc, is perfectly clear. The method we finally adopted is as follows:

An accurately weighed quantity of 0.1 to 0.15 gm. of the menadione, previously dried over sulfuric acid for 3 hours, is placed in a flask, 10 cc. of glacial acetic acid added and followed by 10 cc. of 10 per cent. hydrochloric acid. The contents of the flask is swirled until the menadione is dissolved. About 1 gm. of zinc powder (zinc dust) is then added and the flask closed with a Bunsen valve and allowed to stand in subdued light for ½ hour with occasional agitation. The solution is diluted with some oxygen-free water, then quickly decanted through a pledget of cotton, the reduction flask and

the cotton washed with three 10 cc. portions of oxygen-free distilled water, and the filtrate promptly titrated with tenth-normal ceric sulfate, 0.1 cc. of ortho-phenanthroline T. S. being used as indicator. The results by this method are shown in Table III. In an endeavor to minimize oxidation by air, two of the determinations recorded in this table were made by filling the flasks into which the reduced solutions were filtered with carbon dioxide. This, however, had no material effect on the results.

Reduction with zinc

Sample P. R. S.	99.16%
	99.15
	99.89
	99.19
Sample No. 2704	99.20
	99.33

Table III

We have also used this method for the determination of menadione in 1 mg. coated tablets purchased from a retail pharmacy. A counted number of the tablets equivalent to 10-20 mg. of menadione were finely powdered, avoiding loss during the powdering. The powder was then extracted by maceration and decantation with three 10 cc. portions of chloroform, the residue transferred onto a filter and washed with small portions of chloroform until the washings were colorless. The filtrate and washings contained in a flask were evaporated to dryness at room temperature and in subdued light by means of a current of air drawn through the flask. The residue was dissolved in 5 cc. glacial acetic acid, 5 cc. of 10 per cent. hydrochloric acid added and followed by about 0.5 gm. of zinc powder. The flask was closed with a Bunsen valve and allowed to stand for 20 minutes in the dark. The liquid was diluted with 10 cc. of water, quickly decanted through a pledget of cotton into a flask and the reduction flask and filter washed a few times with 5 cc. portions of oxygen-free water. The filtrate was promptly titrated with fiftieth-normal ceric sulfate and ortho-phenanthroline T. S. as the indicator. One cc. of fiftieth-normal ceric sulfate is equivalent to 1.722 mg. of menadione. The reduction in the first two determinations of Sample No. 1 were made with aluminum without filtration; in all the others with zinc and filtration.

Analysis of tablets claimed to contain 1 mg. of menadione per tablet

	Mg. menadione found per tablet
Sample No. 1	0.99
	0.97
	0.94
	0.95
Sample No. 2	0.95
	0.93

Table IV

As a sort of check on the tablet assays, we ran several determinations with 10 and 15 mg. quantities of menadione in exactly the same manner as the tablets. In addition we also made a few determinations on 10-20 mg. quantities of menadione, previously mixed with 5-15 times its weight of lactose and 2-5 times its weight of starch. These mixtures were thoroughly triturated with a small quantity of diluted alcohol, the liquid allowed to evaporate and then determination made exactly as with the tablets. The recoveries are shown in Table V. In two of the determinations reported in Table V the extraction of menadione was made with carbon tetrachloride instead of chloroform. We prefer, however, to use the latter because of its lower boiling point, and hence the shorter time required for its evaporation.

Determination of 10-20 mg. quantities of menadione alone, and of mixtures with lactose and starch

Menadione alone		*Menadione with lactose and starch*	
Weight of menadione taken	*Weight of menadione found*	*Weight of menadione taken*	*Weight of menadione found*
10.8 mg.	10.9 mg.	15.2 mg.	15.2 mg.
10.7	10.7	17.8	17.6
15.2	15.2	17.2	17.0
12.6	12.6		

Table V

Method II—As explained in the introductory paragraph this is a bromination method. It is applicable to pure menadione, but we have not tried it with pharmaceutic forms such as tablets. The method is carried out as follows: A weighed quantity of about 0.1

to 0.15 gm. of menadione is placed in an iodine flask, 5 cc. carbon tetrachloride added and agitated until the menadione has dissolved. A measured volume of 25 cc. of tenth-normal bromine is then added, followed by 2 cc. of hydrochloric acid. The flask is immediately stoppered, shaken vigorously for 5 minutes and allowed to stand for 1 hour with occasional shaking. Ten cc. of 10 per cent. potassium iodide solution is then added, taking care to prevent escape of bromine, the stopper and the sides of the flask washed down with about 20 cc. of water, and the liberated iodine (excess bromine) titrated with tenth-normal sodium thiosulfate. Starch T. S. may be added near the end. Each cc. of tenth-normal bromine is equivalent to 0.008609 gm. of menadione ($C_{11}H_8O_2$). The tenth-normal bromine should be freshly standardized, using also the same amount of carbon tetrachloride as in the assay and allowing to stand for 1 hour before adding potassium iodide. The determinations by this method are given in Table VI.

Bromination method

Sample	P. R. S.	1 hr. contact with the bromine		99.66%
		2 " " " " "		100.05
		3 " " " " "		100.10
"	No. 2704	1 hr. contact with the bromine		99.69
		2 " " " " "		100.00

Table VI

In our first experiments, not recorded in the table, we used chloroform as the solvent, but for reason not clear to us yet, when the mixture, after adding the bromine solution, was allowed to stand 15 minutes or longer, the results were low and decreased as the time for the reaction was prolonged.

Summary

(1) Two simple procedures are presented for the quantitative determination of menadione.

(2) In procedure I the solution of menadione in glacial acetic acid is reduced with zinc and hydrochloric acid, then titrated with standard ceric sulfate solution and ortho-phenanthroline indicator. This method has also been found reasonably satisfactory for coated tablets of menadione.

(3) According to procedure II, the solution of menadione in carbon tetrachloride is treated with tenth-normal bromine, and the excess of bromine determined in the usual manner with tenth-normal thiosulfate.

ANNOUNCEMENT BY THE NATIONAL FORMULARY COMMITTEE

A RECENT announcement by Dr. Justin L. Powers of Washington, D. C., Chairman of the N. F. Committee, lists ninety-six drugs and preparations which are to be added to the N. F. VII. Deletions number forty-three; some are in this list because of recognition in the U. S. P. XII, others because insufficient use does not justify their continued recognition.

The new articles not previously official in either the U. S. P. or the N. F. are as follows:

Ammoniacal Solution of Silver Nitrate, which is widely used in dentistry for cavity sterilization.

Cherry Juice, required in making Syrup of Cherry.

Chloroformic Solution of Coal Tar.

Compound Elixir of Benzaldehyde, which is for use as a flavoring agent in place of Compound Elixir of Bitter Almond.

Compound Syrup of White Pine with Codeine, replacing the present preparation with morphine.

Magma of Bentonite, a 5 per cent. aqueous suspension for extemporaneous use.

Merbromin, Solution of Merbromin, Surgical Solution of Merbromin. This corresponds to the product originally introduced as Mercurochrome.

Methyl Parahydroxybenzoate, a widely used preservative for preparations used externally.

Neocalamine, Neocalamine Lotion, Neocalamine Ointment and Phenolated Lotion of Neocalamine. A new form of calamine which is more nearly flesh color and its preparations.

Pectin, Pectin Paste, Thin Pectin Paste. Pectin of medicinal grade and preparations of it developed by the late Dr. Fantus for the treatment of indolent ulcers and sores.

Phenothiazine, an anthelmintic showing great promise for veterinary use.

Raspberry Juice, an ingredient of Syrup of Raspberry.

Red Ferric Oxide, used in Neocalamine.

Resorcinol Brown, Solution of Resorcinol Brown. Used in coloring preparations, particularly Solution of Cinchona Alkaloids.

Spirit of Benzaldehyde, for use as a flavoring agent in place of Spirit of Bitter Almond.

Yellow Ferric Oxide, used in the preparation of Neocalamine.

Zinc Eugenol Cement, a preparation used by the dentist in root canal therapy.

ARTICLES DROPPED BY U. S. P. XII AND ADMITTED TO N. F. VII

Acetum Scillae
Acidum Aceticum Dilutum
Aconitum
Acriflavina
Acriflavinae Hydrochloridum
Aethylhydrocupreinae Hydrochloridum
Ammonii Bromidum
Ammonii Salicylas
Arseni Triiodidum
Asafoetida
Bismuthi Subgallas
Calcii Creosotas
Cantharis
Capsicum
Carbromalum
Ceratum Cantharidis
Cinchona
Copaiba
Creosoti Carbonas
Creosotum
Dichloramina-T
Elixir Glycyrrhizae
Emplastrum Cantharidis
Extractum Nucis Vomicae
Ferrum
Fluidextractum Belladonnae Radicis
Guaiacol
Hydrargyri Iodidum Flavum
Iodoform
Kino
Liquor Ammonii Acetatis
Liquor Ferri Chloridi
Liquor Ferri Tersulfatis
Liquor Sodii Hypochloritis Dilutus
Massa Hydrargyri
Mistura Opii et Glycyrrhizae Composita
Oleum Santali
Paraffinum
Paraffinum Chlorinatum
Pepsinum
Pilulae Aloes
Podophyllum
Potassii Chloras
Pulvis Ipecacuanhae et Opii
Pulvis Sennae Compositus
Pyrogallol
Quinina
Resina Podophyli
Santoninum
Scilla
Serpentaria
Sodii Acetas
Spiritus Aethylis Nitritis
Spiritus Benzaldehydi
Spiritus Chloroformi
Strychninae Nitras
Sulfonethylmethanum
Sulfur Lotum
Syrupus Ferri Iodidi
Syrupus Scillae
Theobromina cum Sodii Salicylate
Tinctura Aconiti
Tinctura Cantharidis
Tinctura Capsici
Tinctura Cinchonae Composita
Tinctura Ferri Chloridi
Tinctura Kino
Tinctura Scillae
Tinctura Valerianae
Tinctura Veratri Viridis
Valeriana
Veratrum Viride

ARTICLES OFFICIAL IN N. F. VI BUT ADMITTED TO U. S. P. XII AND THEREFORE NOT ADMITTED TO N. F. VII

Aethylis Carbamas
Amaranthum
Ampullae Bismuthi Subsalicylatis
Ampullae Caffeinae cum Sodii Benzoate
Ampullae Calcii Gluconatis
Ampullae Dextrosi
Ampullae Emetinae Hydrochloridi
Ampullae Epinephrinae Hydrochloridi
Ampullae Hydrargyri Salicylatis
Ampullae Pituitarii Posterioris
Ampullae Quininae Hydrochloridi et Aethylis Carbamatis
Ampullae Sodii Chloridi
Ampullae Sodii Citratis
Calcii Phosphas Praecipitatus
Elixir Phenobarbitali
Liquor Amaranthi
Liquor Dextrosi et Sodii Chloridi Isotonicus
Methylrosanilinum
Potassii Chloridum
Quininae Hydrochloridum
Tabellae Acetophenetidini
Tabellae Acidi Acetylsalicylici
Tabellae Atropinae Sulfatis
Tabellae Barbitali
Tabellae Barbitali Solubilis
Tabellae Codeinae Phosphatis
Tabellae Morphinae Sulfatis
Tabellae Phenobarbitali
Tabellae Sodii Nitritis
Tabellae Sodii Salicylatis
Tabellae Strychninae Sulfatis
Tetrachloroethylenum

ARTICLES OFFICIAL IN N. F. VI BUT NOT ADMITTED TO N. F. VII

Cascara Amarga
Curatio Paraffini
Elixir Amygdalae Compositum
Elixir Aquosum
Elixir Chloralis et Potassii Bromidi Compositum
Fluidextractum Trifolii Compositum
Prunus Cerasus
Rubus Idaeus
Spiritus Amygdalae Amarae
Syrupus Glycyrrhizae
Syrupus Trifolii Compositus

SELECTED ABSTRACTS

From the Current Literature of Science

Sulfathiazole Ointment in the Treatment of Cutaneous Infections. E. L. Keeney, R. H. Pembroke, F. E. Chatard and J. M. Ziegler. *J. A. M. A. 117,* 1415 (1941). Since staphylococcus and to a lesser extent streptococcus are the most frequent invaders of cutaneous lesions, sulfathiazole would seem to be the sulfonamide of choice for local application in an ointment base.

The authors employed an ointment containing 5 per cent. sulfathiazole, prepared by suspending the finely powdered drug in a base consisting of equal parts of hydrous wool fat and vanishing cream. An ointment containing sodium sulfathiazole was likewise tried with no real advantage being observed.

The ointments were tried on patients with infected infantile and adult eczema, impetigo, acne vulgaris, seborrheic dermatitis and other pyrogenic infections of the skin. The ointment was quite effective in all cases and in no case did toxic symptoms develop. In infants receiving applications of the product over one-half the body surface three times a day the concentration of sulfathiazole in the blood ranged from 2.0 to 3.5 mg. per 100 cc. Adults receiving only localized applications did not absorb sufficient sulfathiazole to produce a detectable quantity in the blood. A number of children with infantile eczema became reinfected when a 5 per cent. carbonis detergens ointment was substituted for the sulfathiazole ointment. Sulfathiazole was then incorporated in the carbonis detergens ointment with definite and persistent improvement in the eczema and the infection.

An International Standard for Vitamin E. *Pharm. J. 93,* 150 (1941). An international standard for vitamin E has been announced by the National Institute for Medical Research, London. This is available to laboratories, institutes and research workers throughout the world.

Synthetic racemic alphatocopheryl acetate has been adopted as the standard following a careful study of its chemical, physical and biological properties as well as its suitability as a standard. Fourteen laboratories all over the world co-operated in this study. The international unit for vitamin E was defined as the specific activity of 1 mg. of the standard preparation, this quantity being the average amount which, when administered orally, prevents resorption-gestation in rats deprived of vitamin E. The international standard is issued in the form of a solution in olive oil of which one international unit is contained in 0.1 gm.

The ordinary procedure of submitting a report to the International Conference before setting up the standard was obviously impossible under the present world conditions. However, those members available for consultation and collaboration have assumed the responsibility and established this much needed standard.

The Rate of Diffusion of Sulfonamide Compounds. F. Hawkin. *Quart. J. Pharm. & Pharmacol. 14,* 226 (1941). This study represents a part of a wider study of the behavior of the sulfonamides when inserted into wounds.

Using agar and gelatin gels as laboratory "models" of body tissues and fluids, experiments were conducted to determine the rate of diffusion of various sulfonamides.

In the first group of experiments the diffusion through agar gels plus Ehrlich's reagent was measured. In the first twenty-four hours after a saturated solution has been placed in contact with such agar at 35 degrees C. sulfanilamide travels 4.2 cm., sulfapyridine 2.6 cm., sulfathiazole 2.7 cm., sulfadiazine 2.0 cm., and sulfanilylguanidine 3.1 cm.

In similar experiments using 15 per cent. gelatin gels at 15 degrees C. the concentration per 100 cc., 1 cm. away from the interface after twenty-four hours is: sulfanilamide 31 mg., sulfapyridine 1.5 mg., sulfathiazole 2.2 mg., sulfadiazine 0.45 mg., and sulfanilylguanidine 2.6 mg.

Experiments reported elsewhere would indicate that the penetration of the sulfonamides into living or dead tissues is much less extensive than these figures would suggest.

Variations in Samples of Digitalis Leaves from British Sources. G. M. Watson and W. O. James. *Quart. J. Pharm. & Pharmacol. 14,* 214 (1941). A series of samples of the leaf of Digitalis purpurea was collected in the late summer of 1940 from various places in England and Wales in order to determine whether there was any considerable variation and whether such variation as found might be correlated with environmental and genetic factors.

No simple correlation as to altitude, soil composition etc. with potency was found. Potency varied from 5.5 to 21.2 units per gram, the mean being 12.4. Assays were conducted using the method of the B. P. 1932.

The Stability of Adrenalin in Solutions of Procaine and Adrenalin. By Gerald Woolfe. *Quart. J. Pharm. & Pharmacol. 14,* 234 (1941). A study of a solution of procaine and adrenalin for injection was made using a formula similar to one recently adopted by the Fourth Addendum to the British Pharmacopœia. The formula studied was as follows:

Procaine Hydrochloride	2.0 gm.
Sodium Chloride	0.5 gm.
Parachlormetacresol	0.1 cc.
Solution of Adrenalin Hydrochloride	2. cc.
Sodium Metabisulfite	0.1 gm.
Sterilized Water, to make	100. cc.

Various alterations in this formula were made and the effect on its stability determined. The use of sodium metabisulfite seems essential for the production of a stable solution 0.1 per cent. being the optimum concentration. Storage of the solutions in an inert atmosphere appears to have little influence on stability and it is therefore an unnecessary complication. The substitution of 0.002 per cent. phenylmercuric nitrate for the parachlormetacresol is an improvement and in addition the pH remains higher, e. g. 4.1 as against 3.4. For injection the higher pH is preferable. The method of sterilization recommended is autoclaving at 10-pound pressure for thirty minutes. Although procaine solutions are generally recognized to be unstable if autoclaved, this did not apply to the above solution. Autoclaved solutions containing phenylmercuric nitrate (0.002 per cent.)

lost only 10 per cent. of their activity after a year's storage. Solutions containing parachlormetacresol when autoclaved in vaccine bottles were unstable, which was not the case when the same treatment was given this solution in ampuls.

It is recommended that phenylmercuric nitrate be employed, sterilization accomplished by autoclaving at 10-pound pressure for thirty minutes and the use of ampuls, where possible, in place of vaccine bottles.

Studies on the Relationship Between Diastatic Activity of Saliva and Incidence of Dental Caries. H. J. Florestano, J. E. Faber and L. H. James. *J. A. D. A. 28,* 1799 (1941). Considerable attention has been given to the study of the physicochemical properties of saliva in an attempt to find some factor that might explain or at least be correlated with the development of caries in teeth. In a review of the literature ptyalin has received little attention as a possible factor in dental caries. Gore (*D. Cosmos 77,* 942 (1935)) has shown that salivary ptyalin is capable of hydrolyzing the complex carbohydrate moiety of mucin into simpler sugar which is thus made available for fermentation to lactic acid by acidogenic bacteria present in nearly all mouths. Saliva from carious individuals always was higher in ptyalin content. Hubbell (*Am. J. Physiol. 105,* 436 (1933)) examined the saliva of carious and non-carious children and found no consistent difference in ptyalin content.

In this investigation a number of individuals were studied to compare the incidence of caries with the ptyalin content of the saliva. Saliva from 166 subjects was examined for ptyalin content by a starch iodine technic. At the same time the degree of caries was estimated, dividing the subjects into eight groups based on the extent of caries. The average diastatic index of each group showed a direct relation to the incidence of caries, the greater diastatic activity being accompanied by a higher incidence of tooth decay. The average diastatic index of individuals with rampant caries was three times that of individuals showing no caries. It is suggested that the diastatic activity of saliva be used as an index of susceptibility.

The Rot-proofing of Sandbags. E. F. Armstrong. *Chem. & Ind. 60,* 668 (1941). Sandbags used for protection against bombs and bomb-splinters must of necessity endure for long periods under conditions which favor rotting. This paper is a report of progress

made by a committee in England which studied this problem extensively.

All cellulosic fibers and materials made from them under favorable conditions are subject to attack by micro-organisms and jute from which most sacks are made is no exception. The prime factor of micro-biological attack is dampness or high humidity conditions. Fungi will usually commence to attack at a lower moisture content than that required by bacteria and with jute attack will be negligible if the moisture content is below 17 per cent.

The requirements of a rotproofer are indeed exacting. They are briefly as follows:

1. Must possess fungicidal and bactericidal properties.

2. Should be neither acid nor alkaline.

3. Should be only slightly soluble in water and yet it should evenly and effectively wet the fiber.

4. The substance should not leach out with rain and water.

5. It should not render the bag more inflammable.

6. It should not cause toxicity in workers.

7. The rotproofer must not weaken fiber strength.

8. It must be economical, dry quickly, free from stickiness or oiliness and have no objectionable odor.

9. It should not cause abnormal shrinkage of the bag.

After hundreds of tests only three classes of materials have been found promising. They are:

(1) Specified tar distillates (creosotes).

(2) Organic copper salts.

(3) Cuprammonium.

The type of tar distillate recommended is similar to that for creosoting timber. Copper oleate, stearate and naphthenate belong in group (2). The cuprammonium process is not as favorable due to a weakening action on the fiber.

Full directions for rotproofing using these materials are given and in view of the fact that bags so treated last about two years instead of three months it is quite foolish to use bags in defense work without previous treatment.

SOLID EXTRACTS

A Miscellany of Informative Items, the Sources of Which Are Available on Request

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The adoption by the U. S. P. XII of insulin will guarantee the continued careful control of this very important drug. The insulin patents expire December 24, 1941, and the same control methods used by the Insulin Commission of the University of Toronto which control the patents are to be used in the U. S. P. XII. Over 1,000,000 diabetics in this country alone will thus continue to get the same, safe, standardized product.

AJP

You wouldn't suspect it, but the seemingly prosaic powder known as starch has had 4600 papers about its chemistry printed during the period from 1811 to 1940. A bibliography of these references, both American and foreign, has been compiled and copies have been distributed to thirty-seven university, government and public libraries.

AJP

Castor oil is one of the very few oils having no harmful effect on rubber, or on its rather recently developed synthetic counterpart, neoprene.

AJP

Sulfadiazine continues to score in urinary tract infections, in hemolytic streptococcus infections, and in pneumonia. Mortality averages in the latter illness have been reduced by this chemical, and its seemingly non-toxic, non-nauseating properties makes it appear to approach the ideal sulfonamide drug.

AJP

Some scientists working in the new realm of sulfa-drugs are so pleased with the results they are obtaining in combatting the various cocci that they predict a continuation of research into new fields with comparable results against other types of bacteria as well as viruses.

To complement this month's editorial, we repeat here the findings of an Idaho doctor who made a study of eighty cases of infectious relapse in syphilis. He is of the opinion that the comparative insignificance of mucocutaneous relapse lesions makes their occurrence pass unnoticed more often than not. Two-thirds of such relapse cases have lesions at sites particular favorable for transmission of infection. Eighty per cent. of recurrent lesions appear in the first two years of infection, if treatment is sub-optimal. Two-thirds of the cases of relapse occur within one year after treatment ceases. The frequency of relapse decreases as the number of arsenical injections increases. Irregularity of treatment has some part to play in recurrent lesions. The accepted standard of adequate treatment will not prevent infectious relapse in all cases.

AJP

Once again science makes industry a bit more self-sufficient, for it has devised a substitute for rock wool, asbestos, gypsum or cork, in the form of Perlite, a volcanic rock glass found in abundance in Arizona, and which, after a heat treatment, acts as a splendid insulating agent.

AJP

In Honolulu it's known as the Waikiki Itch. In China it's called Hong Kong Foot. In Europe they call it Tinea. But here in America we know it only too well as Athlete's Foot.

AJP

Oleomargarine comes back into the news and into the American diet through the establishment of a government standard of identity under which the substance may be enriched with a minimum of 9000 units of vitamin A per pound. Vitamin D may be added also, with legal approval. This may be of interest to the alleged 40,000,000 undernourished people in this country, but it will not have much appeal to the dairy farmers.

BOOK REVIEWS

Organic Reagents in Inorganic Analysis. By Ibert Mellan, xxiii+682 pages. Blakiston Company, Philadelphia, Penna., 1941. Price, $9.00.

In this new book, the author has collected the large amount of information available in the literature on the application of organic reagents to the detection and estimation of inorganic substances. An attempt has been made to present this in a convenient and usable form.

The book is in three distinct parts. In the first part (of 24 pages) is presented a brief discussion of the principal types of organic reagents, and of their reactions with inorganic substances. The second section (nearly 200 pages) contains descriptions of over 200 organic reagents considered of importance in the testing of inorganic substances. These are arranged in alphabetical order and include synonyms, empirical and structural formulas, molecular weight, physical constants and solubility. The reactive group and the elements or radicals with which it combines are indicated.

The main portion of the book is devoted to methods of procedure. Directions, in some detail, are given for the detection and estimation of nearly 100 elements or groups. Numerous alternative reagents and procedures are offered for each of these. Throughout the book there are many references to the literature.

Although undoubtedly a valuable reference work, the book has some objectionable features. These include a rather confusing arrangement of references, with much overlapping. A single bibliography would be preferable. There are several errors among the formulas; coordinate bonds in which the metal acts as donor to oxygen, nitrogen, or sulfur are, we believe, rather unusual. The many good points of the book, and the wealth of information it contains will, however, insure its widespread use.

L. A. Reber.

The Chemistry and Manufacture of Cosmetics. By De Navarre D. Van Nostrand Company, Inc., 250 Fourth Avenue, N. Y. 745 pages, including index. Price: $8.00.

According to the author this book was intended as a basic reference or textbook to be of value to cosmetic technicians and students alike. Plaudits are due for it was evidently a tremendous task to collect the enormous amount of factual material for this comprehensive treatise. The subject matter is well organized, facts are presented in orderly fashion, the scope of the book is wide and its finality is verified by the inclusion of certain formula ingredients which have become available in commercial quantities only since the date of issue of the book.

For neophytes in this field, there are many definitions, explanations and theories in the forepart of the book. This material is intended for nothing more than a résumé and may be passed over lightly by anyone familiar with the facts.

The text does not stop with formulas but deals most thoroughly with the scientific and therapeutic phases of cosmetology. There is a maximum of information in adequate detail for a basic understanding of the subject matter. Interspersing the reading matter, there are numerous illustrations, charts, graphs, patent abstracts and literative citations which are comprehensive and interesting. The author wisely places emphasis and devotes ample space to the practical and popular subjects and gives both favorable and unfavorable criticism where his personal experience has made him the wiser. In addition to the practical information presented, there is much subject matter which is thought-provoking. Indeed, this reviewer finished his reading with ideas for a number of practical research problems.

Included in the text is a timely chapter on the regulations and interpretations of the Food, Drug and Cosmetic Act as it relates to cosmetics. In addition to a bibliography arranged according to subject matter, there is a chart entitled "Summaries of the Application Properties of Certified Dyes" which should be of great value to the technician.

This volume can be recommended highly to the student for a standard text, to the pharmacist for new ideas in handling material and compounding, and to the manufacturer who will find it a helpful reference in product formulation.

EDWIN A. MANDEL